REMARKS/ARGUMENTS

Claims 1-52 were pending in the subject application. Applicants have herein canceled claims 1, 3-4, 7 and 39-52 without prejudice. Applicants respectfully note that claim 2 has been amended to include the subject matter of claim 7. In addition, claims 39-52 were of the second medical use format corresponding to claims 1-38. Applicants have also herein amended claims 2, 5-6, and 8-38. This amendment does not involve any issue of new matter. Support for these amendments may be found inter alia in the specification as follows: page 2, lines 11-14; page 9, lines 5-9. Applicants respectfully request entry of the subject amendment such that claims 2, 5-6, and 8-38 will be pending.

Inventorship

Applicants hereby acknowledge for the record the Examiner's statement that the inventorship of the subject application has been changed by adding Slobodon Vukicevic as an inventor.

Information Disclosure Statement

Applicants respectfully submit that copies of each of the references cited in the information disclosure statement filed on November 15, 2002 were submitted to the patent office. Nevertheless, for the Examiner's convenience and to expedite prosecution of the subject application, applicants are submitting courtesy copies of each of the references. A copy of the 1449 form filed on November 15, 2002 is attached as Exhibit I.

Specification

The Examiner stated that an abstract on a separate sheet is required.

In response, applicants respectfully traverse the Examiner's above objection. Applicants contend that an abstract of the disclosure was filed with the application as page 28. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application attach hereto as **Exhibit A** another copy of page 28 of the abstract as filed. Applicants contend that this obviates the Examiner's above objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Oath/Declaration

The Examiner stated that the oath or declaration is defective because it allegedly refers to U.S. Serial No. 08/445,328, and not U.S. Serial No. 09/445,328.

In response, applicants attach hereto as **Exhibit B** a substituted executed declaration and power of attorney which refers to U.S. Serial No. 09/445,328. Applicants contend that this obviates the Examiner's above objection.

Rejection Under 35 U.S.C. '102

The Examiner rejected claims 2, 5-14, 27 and 35-38 under 35 U.S.C. §102(b) as being anticipated by Kubersampath.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants respectfully point out that claim 2 recites as follows: "[a] method of delaying the need for, or reducing the frequency of, dialysis treatments of a mammal **afflicted with acute renal failure**, the method comprising administering to said mammal a therapeutically effective amount of a OP/BMP renal therapeutic agent comprising a polypeptide comprising a sequence at least 70% homologous to the C terminal seven-cysteine domain of human OP-1, the sequence of the C terminal seven-cysteine domain of human OP-1 being set forth at residues 330-431 of human OP-1." [emphasis added]. Applicants respectfully remind the Examiner that anticipation "requires the disclosure in a single prior art reference of each element of the claim under consideration." *W.L. Gore & Assocs. V. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983). While Kubersampth may describe treatments for loss of bone bass, and refer to chronic renal failure, it does not mention acute renal failure, let alone discuss treatments for acute renal failure using an OP/BMP. In particular, it does not describe the use of a renal therapeutic agent comprising a polypeptide comprising a sequence at least 70% homologous to the C terminal seven-cysteine domain of OP-1, the sequence of the C terminal seven-cysteine domain of OP-1 being set forth at residues 330-431 of human OP-1 to delay the need for, or reduce the frequency of, dialysis treatments of a mammal afflicted with acute renal failure. Applicants contend that these amendments and remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. '103

The Examiner rejected claims 2, 15-20, 24 and 35-38 under 35 U.S.C. §103 as being unpatentable over Kubersampath (AH) in view of Anderson. The Examiner also rejected claims 2, 23-24 under 35 U.S.C. §103 as being unpatentable over Kubersampath (AH) in view Spragg, Saavedra and Kubersampath (AG).

In response, applicants respectfully traverse the Examiner's above rejection. Applicants point out that the Examiner had not rejected claim 7. Claim 2 has been amended to recite language of claim 7, reciting: "A method of delaying the need for, or reducing the frequency of, dialysis treatments of a mammal afflicted with acute renal failure, the method comprising administering to said mammal a therapeutically effective amount of a renal therapeutic agent comprising a polypeptide comprising a sequence **at least 70% homologous to the C terminal seven-cysteine domain of human OP-1, the sequence of the C terminal seven-cysteine domain of OP-1 being set forth at residues 330-431 of human OP-1**." [emphasis added]. Applicants contend that these amendments and remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. 112, first paragraph

The Examiner rejected claims 2, 5, 7-20, 23, 24, 27 and 35-38 as allegedly not enabled, stating that the specification does not reasonably provide enablement for a method of treatment comprising administering the other OP/BMP renal therapeutic agents recited in the claims.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the claims are fully enabled. First, applicants point out that claim 2 has been amended to recite in part "polypeptide comprising a sequence at least 70% homologous to the C terminal seven-cysteine domain of human OP-1, the sequence of the C terminal seven-cysteine domain of OP-1 being set forth at residues 330-431 of human OP-1." Accordingly, the morphogens recited in the claims each would comprise a sequence which is at least 70% homologous to the C terminal seven-cysteine domain of human OP-1. Applicants contend that the claimed invention is enabled. In support, applicants attach hereto as **Exhibit C** a reference by Guo *et al.* which demonstrates that other morphogens encompassed by the 70% homology terminology also

possess an OP-1-like activity. Specifically, Guo *et al.* show that other morphogens, including OP-2 (also referred to as BMP-8), BMP-5, BMP-6 (also referred to as Vgr1), Drosphila 60A, BMP-2, BMP-4 and Drosophila decapentaplegic (dpp) have been found to have similar biological effects as OP-1. *See* Guo et al, page 131.

Pursuant to MPEP 2164.01, "Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." Thus, the test of enablement is whether a skilled artisan can practice the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Guo provides evidence that, just like OP-1, a number of morphogens with diverse sequences (OP-1, OP-2, BMP-5, BMP-6 and 60A, and those within the subgroup containing BMP-2, BMP-4, and Dpp) all have similar biological effects. See Guo et al., page 131. Especially worth mentioning is the fact that human BMP2 shares only about 24.5% overall sequence identity with human OP-1 (**Exhibit D**), yet has been shown, similar to BMP-7 (*i.e.* OP-1), to provide protection against renal ischemia-reperfusion injury. (**Exhibit E**) A close analysis of the conserved C-terminal Cys domain sequences (**Exhibit F**) reveals that the these sequences share about 78% sequence homology in this region, indicating that the conserved C-terminal Cys domain sequence is likely important for the observed common biological function. In addition, **Exhibits G and H** also indicate that the C-terminal Cys structures are the most conserved regions among all morphogens, while the more N-terminal sequences are very diverse. One extreme example is the *Drosophila* protein Dpp, which contains large numbers of amino acid sequence "insertions" at the N-terminal regions such that it is only about 40% identical to its closest relatives human BMP-2 and -4. However, it is remarkably conserved at the C-terminus so that it is about 75% identical to human BMP-2 and -4, and 58% identical to human OP-1. The only reasonable interpretation of these data is that the conserved Cys domain sequence defines the common structural feature important for their common biological functions. Therefore, it can be reasonably expected that other morphogens, especially those within the subgroup containing OP-1, OP-2, BMP-5, BMP-6, and 60A, and those within the subgroup containing

BMP-2, BMP-4, and Dpp, will also exhibit an OP-1-like activity in the claimed invention. In view of these data, a skilled artisan would reasonably conclude that the specification enables the claimed invention. Applicants contend that these amendments and remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. 112, second paragraph

The Examiner rejected claims 2, 15-20, 23, 24, 27 and 35-38 as indefinite because they recite the term "OP/BMP renal therapeutic agent." The Examiner states that the instant specification does not identify the material element or combination of elements which is definitive of an OP/BMP.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have herein amended the claims. Each of the claims now recites (either directly or as a dependent claim) a "polypeptide comprising a sequence at least 70% homologous to the C terminal seven-cysteine domain of human OP-1, the sequence of the C terminal seven-cysteine domain of OP-1 being set forth at residues 330-431 of human OP-1." Applicants note that previous claim 7 which recited similar language was not rejected on the above grounds. Applicants contend that this amendment obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner rejected claims 5, 6 and 13 as indefinite over the recitation "A C-terminal cysteine domain" alleging that it is unclear if such domain or some portion of the domain is intended. The Examiner also rejected claims 7-13 as indefinite over the recitation "an amino acid sequence of a seven cysteine domain" alleging that it is not clear if the amino acid sequence of the seven cysteine domain or some portion of the domain is intended.

In response, applicants respectfully traverse this ground of rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have herein amended the claims. Each of the claims now recites (either directly or as a dependent claim) a "polypeptide comprising a sequence at least 70% homologous

to the C terminal seven-cysteine domain of human OP-1, the sequence of the C terminal seven-cysteine domain of OP-1 being set forth at residues 330-431 of human OP-1." Accordingly, the claim sets forth the amino acid positions for the amino acid residues which comprise the seven cysteine domain of human OP-1. Applicants contend that the metes and bounds of the claim are clearly set forth.

Obviousness-type Double Patenting

The Examiner rejected claims 2, 5-20, 23, 24, 27 and 35-38 under the judicially created doctrine of obviousness-type double patenting over the claims U.S. Serial No. 08/851,628. In response, applicants respectfully note that this is a provisional double patenting rejection since both the subject application and U.S. Serial No. 08/851,628 are pending. Accordingly, applicants contend that nothing is necessary at this time and that the Examiner may continue to maintain the rejection until both cases are ready to issue. *See* MPEP 804 ("The 'provisional' double patenting rejection should continue to be made by the Examiner in each application as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining in one of the applications. If the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the Examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent. If the 'provisional' double patenting rejections in both applications are the only rejections remaining in those applications, the Examiner should then withdraw that rejection in one of the applications (*e.g.*, the application with the earlier filing date) and permit the application to issue as a patent. The Examiner should maintain the double patenting rejection in the other application as a 'provisional' double patenting rejection which will be converted into a double patenting rejection when the one application issues as a patent.")

The Examiner rejected claims 2, 5-20, 23, 24, 27 and 35-38 under the judicially created doctrine of obviousness-type double patenting over the claims of U.S. Patent No. 6,498,142. In response, applicants point out that the claims of 6,498,142 relate to chronic renal failure. In contrast, the pending claims in the subject application relate to acute renal failure. Accordingly, applicants

contend that an obviousness-type double patenting rejection is improper and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

No fee is deemed necessary in connection with this amendment. However, if any fee is necessary, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 18-1945, under order No. JJJ-P01-514.

Dated: June 16, 2003

Respectfully submitted,

By_____

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